NHLBI-ACTIV Response to COVID-19: Accelerating Therapeutic Interventions

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NHLBI-NIH Strategic Approach to Addressing COVID-19

Goals

Goals	
Reduce case severity/fatality, speed recovery	Host-Directed Therapeutics Clinical Trials
Understand short- and long-term trajectory	Observational/Longitudinal Studies
Enable risk stratification, precision interventions	Translational/Pre-Clinical Studies
Identify biomarkers and therapeutic targets	Data Resources and Platforms
Target populations most severely affected	Community-Engaged Research

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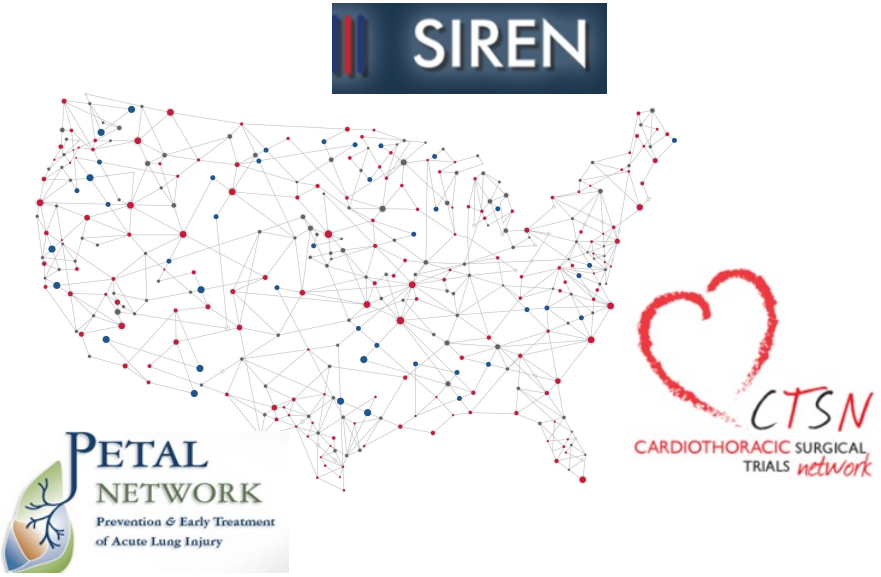
NHLBI's "Network of Networks" (CONNECTS): Integration into the NIH ACTIV Trial Infrastructure

ACTIV

CONNECTS

Goal: Leverage and expand NHLBI's national clinical research networks to rapidly and nimbly respond to emerging research and clinical needs for COVID-19

- **Leverages existing assets**, data, and studies
- Creates a comprehensive, **expandable platform** that links trial network, registries, and cohorts
- Facilitates case finding, **clinical trial accrual,** and **community engagement**



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NHLBI-NIH COVID-19 Therapeutics Portfolio: Rapid Response Featuring Adaptive Clinical Trial Protocols

PREVENTION | ASYMPTOMATIC | SYMPTOMATIC | ED | HOSPITAL | ICU | RECOVERY | RECOVERED

Host-Directed Therapeutics Clinical Trials & Case Registries

Patient Populations	Pre-hospital Outpatient	Hospitalized Patients (+/- ventilatory support)	Post-hospital Convalescent Patients
Anti-Inflammatory	**COLCORONA Colchicine**	**ORCHID Hydroxychloroquine**	
Passive Immunity	**C3P0 – Convalescent Plasma**	**ACTIV – 3 Monoclonal Antibodies**	
Tissue Injury Repair		**ACTIV – 4 RAAS**	
Anti-Thrombotic	**ACTIV – 4B**	**ACTIV – 4A**	**ACTIV – 4C**

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Testing Re-Purposed Anti-inflammatory Treatments for COVID-19 Outpatients: COLCORONA Trial

PREVENTION | ASYMPTOMATIC | **SYMPTOMATIC** | ED | HOSPITAL | ICU | RECOVERY | RECOVERED

Can colchicine prevent complications due to inflammation in outpatients?

Patient Populations

- Non-hospitalized patients
- 40 years old and older
- At least one high-risk characteristic

Anti-Inflammatory

- Colchicine or placebo for 30 days

ColCorona

Primary Endpoint of Hospitalization or Death

Colchicine (n=2075)	Placebo (n=2084)	Odds ratio (95% CI)	p value
96 (4·6%)	126 (6·0%)	0·75 (0·57–0·99)	0·042

Published in *The Lancet*

Benefit of colchicine observed among outpatients with confirmed COVID-19

Tardif, et al. 2021. *The Lancet. Resp med*, S2213-2600(21)00222-8.

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Determining the Effectiveness of Hydroxychloroquine Treatment in Hospitalized COVID-19 Patients: ORCHID Trial

PREVENTION | ASYMPTOMATIC | SYMPTOMATIC | ED | **HOSPITAL** | ICU | RECOVERY | RECOVERED

Hydroxychloroquine was promoted as a COVID-19 treatment but lacked safety and efficacy data

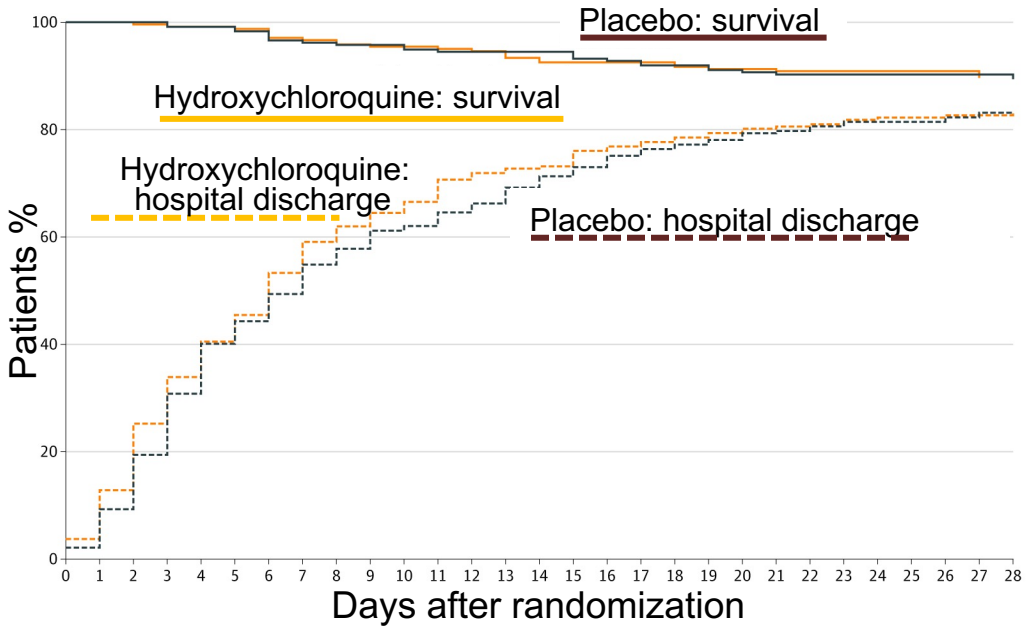
Patient Populations

- Adults hospitalized with respiratory symptoms
- Median age 57 years
- **37% Hispanic; 23% Black**

Anti-Inflammatory

- Hydroxychloroquine or placebo

Survival and Hospital Discharge Following Randomization



PETAL NETWORK
Prevention & Early Treatment of Acute Lung Injury

Hydroxychloroquine treatment demonstrated ***no benefit or harm*** *to COVID-19 inpatients*

Published in *JAMA*

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Self WH et al., *JAMA,* 2020

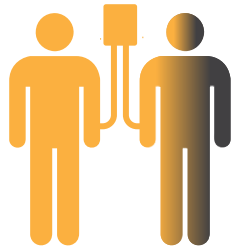
Convalescent Plasma Treatment for Outpatients with COVID-19: C3PO Trial

PREVENTION | ASYMPTOMATIC | **SYMPTOMATIC** | **ED** | HOSPITAL | ICU | RECOVERY | RECOVERED

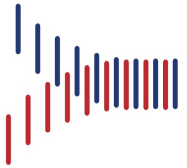
Seek low-cost options for outpatients at risk for severe COVID-19: few RCTs with CP for other illnesses

CONNECTS

Patient Populations	• ED patients with mild to moderate symptoms for ≤1 week • ≥1 risk factor associated with severe COVID-19
Passive Immunity	• Single dose of convalescent plasma *or* • Saline placebo



C3PO
Clinical Trial of COVID-19 Covalescent Plasma in Outpatients



SIREN

*Interim analysis found convalescent plasma has **no significant benefit** or harm; study enrollment stopped early*

Registered with ClinicalTrials.gov: NCT04355767

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Antithrombotic Strategies to Prevent COVID-19 Complications in Hospitalized Patients: ACTIV-4A

PREVENTION | ASYMPTOMATIC | SYMPTOMATIC | ED | **HOSPITAL** | ICU | RECOVERY | RECOVERED

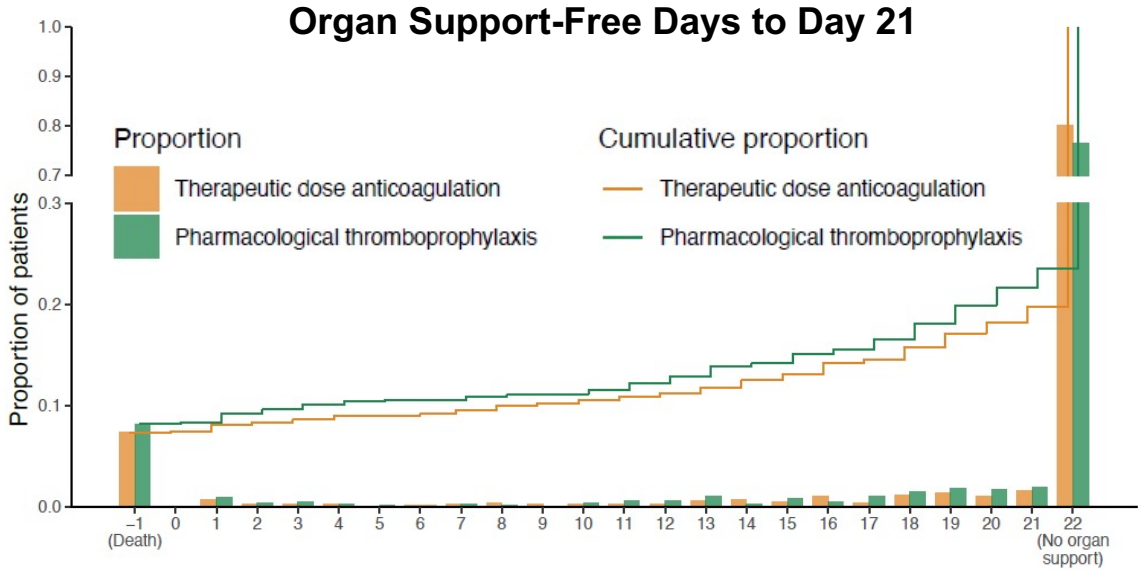
Blood clots and inflammation are common complications in COVID-19 patients

REMAP-CAP

ACTIV-4 Acute Inpatient Anti-Thrombotic Study

ATTACC

Patient Population	• Hospitalized patients • Stratified by severe or moderate illness
Anti-Thrombotic	• **Therapeutic dose** of heparin • **Prophylactic dose** of heparin



Therapeutic dose of anticoagulant helps moderately ill but not critically ill inpatients

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. medRxiv 2021.05.13.21256846; doi: https://doi.org/10.1101/2021.05.13.21256846

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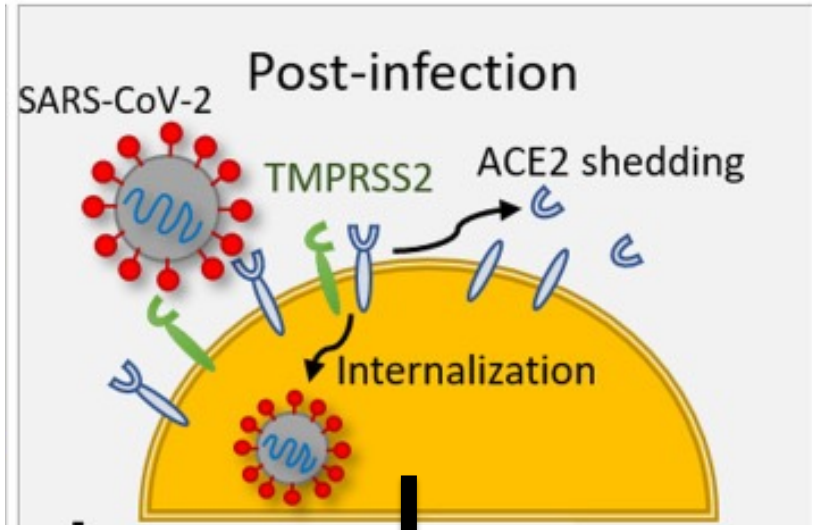
Working Hypothesis: Imbalance in the Renin-Angiotensin-Aldosterone System (RAAS) Modulates COVID-19 Clinical Course

SARS-CoV-2 leads to host tissue injury, increases pro-inflammatory, pro-thrombotic and pro-fibrosis signaling



↑ Inflammation
↑ Thrombosis
↑ Fibrosis

ACTIV-4

Patient Populations

Hospitalized Patients

Tissue Injury Repair

ACTIV – 4 RAAS

Test whether **RAAS targeting drugs** can prevent severe COVID-19 responses including:

- **Vascular Injury**
- **Pro-thrombotic**
- **Inflammatory**
- **Fibrotic**

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Adapted from Goldin et al., *Transl Med Commun.,* 2020 and Ingraham et al., *Eur Respir J.,* 2020

Evaluating Effectiveness of Antithrombotic and RAAS-Targeting Drugs to Reduce Life-Threatening Complications

Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 (ACTIV-4)

COVID-19 Progression →

PREVENTION → ASYMPTOMATIC → SYMPTOMATIC → ED → HOSPITAL → ICU → RECOVERY → RECOVERED

Patient Populations	Pre-hospital Outpatient	Hospitalized Patients	Post-hospital Convalescent Patients
Anti-Thrombotic	ACTIV – 4B	ACTIV – 4A	ACTIV – 4C
	• **Anticoagulation (apixaban)** • **Antiplatelet agent**: aspirin • **Placebo**	• **Prophylactic dose** of heparin • **Therapeutic dose** heparin	• **Prophylactic dose** anticoagulant • **Therapeutic dose** anticoagulant
Tissue Injury Repair		ACTIV – 4 RAAS Renin-angiotensin-aldosterone system targeting drugs	

CONNECTS

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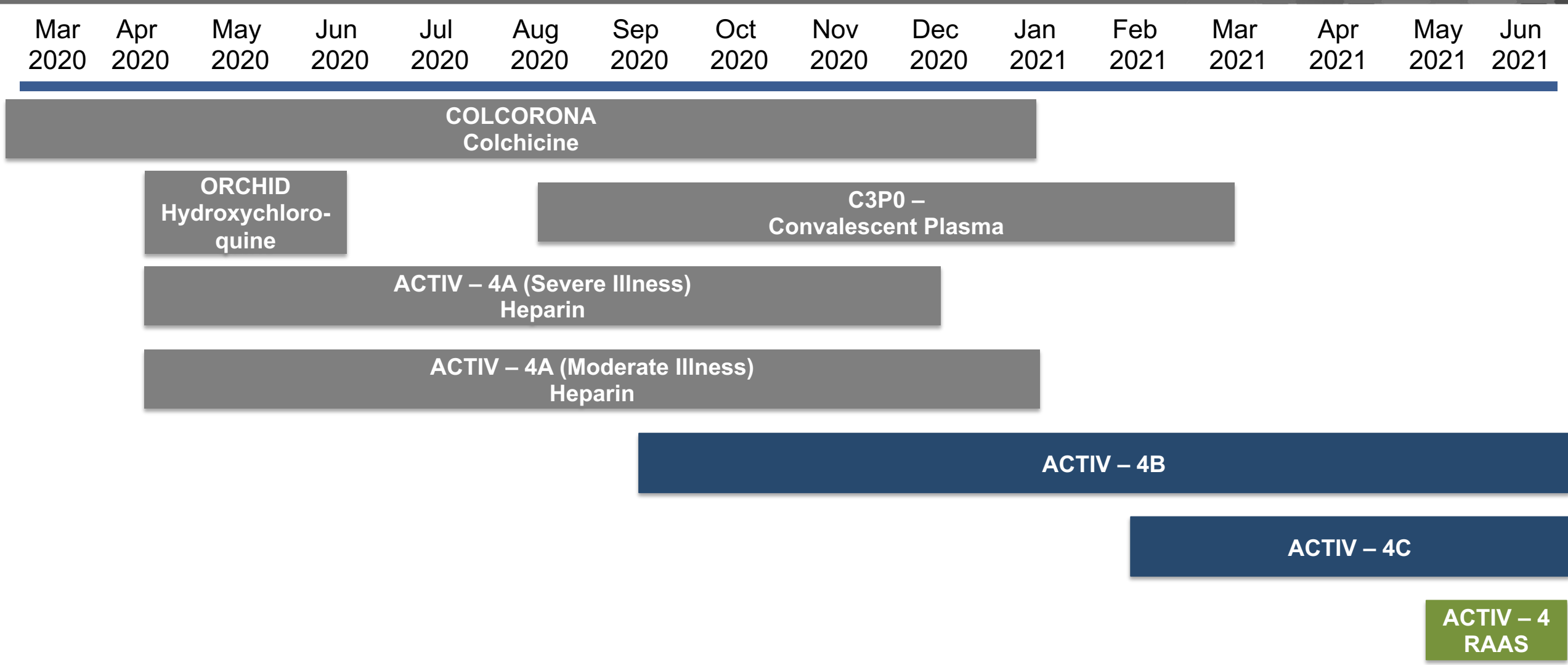
NHLBI-NIH COVID-19 Rapid Adaptive Clinical Trials of Therapeutics: Impact on Clinical Practice



NIH Ecosystem Addressing COVID-19 Clinical Challenges: Accelerating COVID-19 Therapeutic Interventions